

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

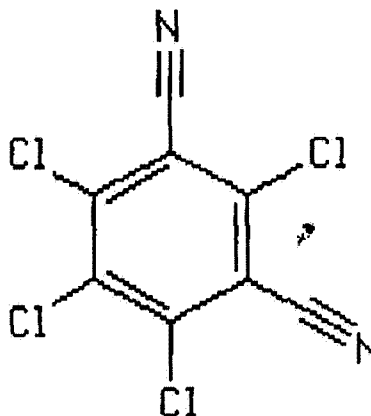
013132

\* REVISED 11/13/96

Chemical Name: Chlorothalonil

PC Code: 081901

Structure



The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for Chlorothalonil at a meeting held on November 7, 1996. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments. **This revision reflects the review of the toxicology data base which included the recently submitted 21-day dermal toxicity study in rats.**

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

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## DERMAL ABSORPTION DATA

MRID: 43600103

% absorbed: 5%

An upper limit of 5% was estimated based on studies in the rat. This dermal absorption rate is to be used for all chlorothalonil exposure scenarios except the use in paints and stains containing chlorothalonil. For these scenarios, a 1.22% dermal absorption rate (8-hour period) for latex based paints and a 1.34% dermal absorption (8 hour period) for alkyl-based stains are suggested. These values are based on the dermal absorption studies submitted on these products. The 8-hour rate was selected since it is assumed professional painters wash with soap and water using latex paint and paint thinners after using the alkyl stains (Memo. R. Zendzian, TB-I to M. Clock, RCAB dated 9/15/95).

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## ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - Guideline No.: Subchronic dietary toxicity - rat §82-1a

MRID No.: 40243702

Summary: In a subchronic study, one group of male Fischer 344 rats received chlorothalonil (technical) in their diet at 175 mg/kg/day (only dose tested) for 3 months. Following serial sacrifices on days 4 and 7, and study weeks 2, 4, 6, 8, 10, 12 and 13 of exposure, the kidneys and stomach underwent histopathological examinations.

Dose and Endpoint for use in risk assessment: 175 mg/kg/day based on renal and gastric lesions observed within four days of dosing. However, since an Uncertainty Factor of 300 (see Comments below) is used, the dose to be used for risk assessment should be 0.58 mg/kg/day ( $175 \text{ mg/kg/day} \div 300 = 0.58 \text{ mg/kg/day}$ )

Comments about study and/or endpoint: The lesions observed in this study appeared to be precursors to kidney and forestomach lesions observed following chronic dietary administration in rats and mice.

Since only one dose level was tested and effects were seen at this dose (LOEL), an extra Uncertainty Factor of 3 was added to the conventional Uncertainty Factor of 100 for risk assessments (i.e, for a total of 300).

**This risk assessment is required.**

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## SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

Study Selected - Guideline No.: 21-day dermal toxicity - rat §82-2

MRID No.: 44119101

Summary: In a dermal toxicity study, male Fischer 344 rats (10/group) received 15 repeated dermal applications of chlorothalonil (98.1%) at 60, 100, 250 or 600 mg/kg/day, 6 hours/ day for 5 days/week during a period of 21 days. The vehicle control group received 0.2% aqueous methyl-cellulose (2.4 ml/kg) on the same schedule. There was no mortality. Clinical signs at doses  $\leq$  100 mg/kg/day were limited to rough hair coat and colored material around the nose and/or eyes. Dermal irritation, characterized as erythema and desquamation, was observed at all dose levels. No systemic toxicity was observed. Treatment-related dermal lesions were hyperkeratosis and hyperplasia of the squamous epithelium of all rats at all dose levels.

Dose and Endpoint for use in risk assessment: NOEL = 600 mg/kg/day (HDT); no systemic toxicity was observed at the highest dose tested.

Comments about study and/or endpoint: The objective of this study was to establish a NOEL for kidney effects after dermal administration as the kidney was the target organ following oral administration to rats and dogs. However, results of this study indicate that kidneys are not the target organ after dermal applications at doses up to and including 600 mg/kg/day.

**This risk assessment is required.**

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## INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

Study Selected - Guideline No.: 21-day dermal toxicity - rat §82-2

MRID No.: 44119101

Summary: See Short-term

Dose and Endpoint for use in risk assessment: NOEL = 600 mg/kg/day (HDT); no systemic toxicity was observed at the highest dose tested.

Comments about study and/or endpoint: The objective of this study was to establish a NOEL for kidney effects after dermal administration as the kidney was the target organ following oral administration to rats and dogs. However, results of this study indicate that kidneys are not the target organ after dermal applications at doses up to and including 600 mg/kg/day.

**This risk assessment is required.**

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**CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)**

Study Selected - Guideline No.: Chronic toxicity/carcinogenicity study - rat §85-1

MRID No.: 41250502

Summary: In combined chronic toxicity/carcinogenicity study, Fischer 344 rats (65/sex/dose) were administered diets containing chlorothalonil (98.3%) at 0, 2, 4, 15 or 175 mg/kg/day for up to 111 weeks. No treatment-related effects were seen at 2 mg/kg/day dose groups. At 4 mg/kg/day chlorothalonil caused slight increases in kidney weights and histopathological lesions in the kidneys and stomach of both sexes of rats. Treatment-related effects at 15 mg/kg/day were: alterations in clinical chemistry and urinalysis; changes in absolute and relative kidney weights; preneoplastic lesions (hyperplasia) in the kidneys and chronic irritation of the forestomach. At 175 mg/kg/day chlorothalonil included increased mortality, kidney weights and parathyroid enlargement, and decreased body weight and food consumption relative to body weight were noted in both sexes as compared to the control. Histopathology revealed increased renal tubular adenomas and carcinomas in association with the hyperplastic lesion in males at 4.0 mg/kg/day and in both sexes at 15 mg/kg/day and 175 mg/kg/day groups. There was a dose-related increase in the incidence and/or severity of hyperplasia, hyperkeratosis and ulcers or erosions of the squamous mucosa of the forestomach in both sexes at 4, 15 and 175 mg/kg/day when compared to controls. Neoplastic lesions observed in the stomach were: papillomas of the squamous mucosa of the forestomach at 4 mg/kg/day as well as papillomas and carcinomas at 4, 15 and 175 mg/kg/day. Lesions in the forestomach were considered to be the result of chronic irritation of the gastric mucosa by chlorothalonil.

Dose and Endpoint for use in risk assessment: NOEL = 2.0 mg/kg/day based on increased kidney weights, hyperplasia of the proximal convoluted tubule, forestomach hyperplasia and ulcers at 4 mg/kg/day.

Comments about study and/or endpoint: This study was used to establish the RfD. The NOEL specified above will be used for risk assessment for non-cancer effect and the Q<sub>1</sub>\* will be used in the risk assessment for the carcinogenic endpoint. Since an oral study was used, the dermal absorption factor should be used in risk assessments.

**This risk assessment is required.**

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## INHALATION EXPOSURE (ANY TIME PERIOD)

Except for an acute inhalation toxicity study, no inhalation toxicity studies were available for this assessment. Based on the  $LC_{50}$  value of 0.092 mg/L, chlorothalonil is placed in Toxicity Category II. Therefore, risk assessment should be inclusive of the inhalation (100% absorption) plus dermal (5% absorption) exposures. The inhalation exposure should be combined with the dermal exposure and the total exposure should be compared to the dermal NOEL in obtaining the Margin of Exposure.

This risk assessment is required.

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## CANCER CLASSIFICATION AND BASIS: B2

$$Q_1^* = 7.66 \times 10^{-3} (\text{mg/kg/day})^{-1}$$

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RfD AND BASIS: 0.02 mg/kg/day based on increased kidney weights, hyperplasia of the proximal convoluted tubule, forestomach hyperplasia and ulcers at 4 mg/kg/day.

NOEL for critical study: 2 mg/kg/day

Study type - Guideline No.: Chronic toxicity/carcinogenicity study - rat §83-5

MRID No.: 41250502

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## ACUTE TOXICITY ENDPOINTS:

### Acute Toxicity of Chlorothalonil

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	00094941	$LD_{50} = > 1000 \text{ mg/kg}$	IV
81-2	Acute Dermal	00094940	$LD_{50} = > 1000 \text{ mg/kg}$	IV
81-3	Acute Inhalation	00094942	$LC_{50} = 0.094 \text{ mg/L (M)}$ $0.092 \text{ mg/L (F)}$	II
81-4	Primary Eye Irritation	00246769	Severe irritant	I
81-5	Primary Skin Irritation	00094939	Slight irritant	IV
81-6	Dermal Sensitization	40546001	Non-sensitizer	NA